Aspartame Does Not Affect Aminergic and Glutamatergic Receptor Kinetics in Rat Brain

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Chronic exposure to antagonists or agonists can up- or down-regulate neurotransmitter receptors. Changes in central nervous system (CNS) receptors might underlie adverse reactions anecdotally attributed to ingestion of aspartame (L-aspartyl-L-phenylalanine methyl ester, APM). This high-intensity sweetener is metabolized in the gastrointestinal tract to phenylalanine, which is absorbed into the circulatory system. Phenylalanine and its metabolite tyrosine compete with tryptophan for transport into brain, where levels of these amino acids may influence the synthesis of the aminergic neurotransmitters norepinephrine, dopamine, and serotonin. The influence of postprandial variation in plasma amino acid levels and of food additives that may affect plasma amino acids deserves careful attention. Phenylalanine with its known neurotoxic effects in phenylketonuria is of special interest. This paper reports the lack of effect of prolonged APM administration on several neurotransmitter receptor systems in brain of adult and weanling rats.

Adult male Sprague-Dawley rats were given APM 500 mg/kg daily for 30 days in their drinking water. By use of standard receptor assay procedures,[1,2] the binding kinetics for adrenergic, dopaminergic, and serotonergic receptors were determined in appropriate brain regions (TABLE 1). Brain content of the aminergic neurotransmitters and their major metabolites was measured, as were plasma and brain levels of phenylalanine, tyrosine, and other amino acids. Neither receptor kinetics (K_d and B_{max}), nor neurotransmitter content, nor levels of phenylalanine and tyrosine in plasma and brain were altered.

Because of the greater vulnerability of the immature mammalian brain to neurotoxic action, studies for possible effects of APM on CNS aminergic function were done in weanlings (age 20 to 22 days) born to rats given APM 500 mg/kg daily in drinking water throughout gestation and lactation. No CNS effect of APM exposure was found in aminergic receptor kinetics (TABLE 1), levels of neurotransmitters and metabolites, or in plasma levels of phenylalanine and tyrosine. However, small but significant decreases occurred in brain levels of phenylalanine, glutamate, and aspartate. Subsequent studies found no effect of perinatal APM exposure on glutamatergic binding (TABLE 1), but decreases in glutamate and aspartate were again observed in cerebral cortex and hippocampus (TABLE 2). After termination of exposure to APM, levels of these excitatory amino acids returned to normal within three weeks (TABLE 2).

We conclude that prolonged high-dose APM ingestion does not affect aminergic or glutamatergic receptor kinetics in brain of adult or weanling rats.[1-3] Because APM administration in drinking water did not significantly affect plasma levels of amino acids, these findings are not unexpected. However, the possible effects of significant changes in plasma amino acids levels require close attention.

TABLE 1. Receptor Kinetics in Rat Brain

Receptor	Control		APM (500 mg/kg daily)	
	K_d	B_{max}	K_d	B_{max}
Adrenergic α_1				
Adult	0.05 ± 0.01	203 ± 11	0.04 ± 0.01	215 ± 25
Adrenergic α_2				
Adult	2.5 ± 0.02	115 ± 8	2.1 ± 0.3	100 ± 11
Weanling	1.5 ± 0.04	143 ± 3	1.4 ± 0.06	29 ± 5
Serotonergic 5-HT_{1A}				
Adult	2.2 ± 0.3	167 ± 14	2.6 ± 0.6	163 ± 20
Serotonergic 5-HT_2				
Adult	0.54 ± 0.04	269 ± 34	0.60 ± 0.10	284 ± 54
Weanling	0.33 ± 0.02	281 ± 15	0.43 ± 0.04	251 ± 17
Dopaminergic D_1				
Adult	0.55 ± 0.1	780 ± 54	0.60 ± 0.10	806 ± 62
Weanling	0.35 ± 0.03	852 ± 54	0.39 ± 0.01	743 ± 55
Dopaminergic D_2				
Adult	0.06 ± 0.01	279 ± 15	0.05 ± 0.01	250 ± 17
Weanling	0.056 ± 0.005	307 ± 15	0.054 ± 0.004	256 ± 22
Glutamatergic NMDA				
Weanling				
Cortex	2.64 ± 0.17	1.82 ± 0.12	3.11 ± 0.48	1.58 ± 0.17
Hippocampus	4.49 ± 0.88	1.99 ± 0.20	5.41 ± 0.57	1.80 ± 0.20
Total glutamatergic				
Weanling				
Cortex	843 ± 119	35.3 ± 6.7	941 ± 60	37.3 ± 3.2
Hippocampus	537 ± 54	18.9 ± 3.1	534 ± 42	26.9 ± 3.5

NOTE: Dopaminergic receptor kinetics were determined in striatum, serotonergic 5-HT_{1A} kinetics in hippocampus, and all others in cerebral cortex except where otherwise noted.

K_d values represent nM concentrations; B_{max} values are fmol/mg protein, except for glutamatergic receptors, where B_{max} values are pmol/mg protein. Values are means ± SEM for 6–12 individual Scatchard determinations. No K_d or B_{max} comparison (APM treatment vs. control) yielded a statistically significant difference (Student's *t* test).

Abbreviations: APM, L-aspartyl-L-phenylalanine methyl ester; NMDA, *N*-methyl-D-aspartate.

TABLE 2. Glutamate and Aspartate Levels in Cerebral Cortex and Hippocampus of Rats after Maternal Ingestion of Aspartame[a]

Region	Amino Acid	Control	APM Exposure
At time of weaning			
Cerebral cortex	Glutamate	9050 ± 260	8230 ± 210[b]
	Aspartate	3720 ± 100	3240 ± 130[b]
Hippocampus	Glutamate	9250 ± 230	8370 ± 290[b]
	Aspartate	2870 ± 140	2790 ± 110
Three weeks after termination of aspartame			
Cerebral cortex	Glutamate	8820 ± 260	10400 ± 1080
	Aspartate	2950 ± 130	3150 ± 83
Hippocampus	Glutamate	8470 ± 540	9640 ± 870
	Aspartate	2010 ± 170	2010 ± 53

[a]Values represent nmol/g tissue and are means ± SEM of five rats per group.

[b]Differences in control vs. APM, $p < 0.05$; all others, not significant (Student's *t* test). APM, L-aspartyl-L-phenylalanine methyl ester.

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